REMARKS

Applicants submit these remarks in response to the Office Action dated February 25, 2003. Claims 23-38 are pending and have been amended as discussed below. No new matter is added.

Claims 23-35 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Reconsideration and withdrawal of this rejection are respectfully requested for the reasons discussed below.

Claim 25 allegedly is indefinite for reciting polynucleotide sequences. This has been addressed by amendment herein. Claims 35 allegedly is indefinite for reciting the isolated nucleic acid of claim 25, wherein the polynucleotide comprises SEQ ID NO:1, but claim 35 recites a polypeptide with at least one conservative mutation. This has been addressed by amendment herein.

Claims 23 and 25-38 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly is not enabling for any nucleic acid encoding SEQ ID NO:2 or fragments thereof, a polynucleotide 90% identical to SEQ ID NO:2, the complement of these sequences, or polynucleotides encoding a polypeptide with up to 50 substitutions in the sequence. The Examiner reviewed the factors to be considered, citing *In re Wands*, 858 F.2d 731, 738 (Fed, Cir. 1988). The Examiner further stated that although the specification discloses differential expression of SEQ ID NO:1 in prostate cancer cells and normal prostate cells, this use allegedly would not correlate with variants of SEQ ID NO:1 or with a polypeptide of SEQ ID NO:2 encoded by such variant polynucleotides. Regarding the identity of SEQ ID NO:2 as a tetraspan protein, the Examiner states that it is not evident that a polypeptide of SEQ ID NO:2 possesses all the structural characteristics of tetraspan proteins. Finally, the Examiner notes that some tetraspan protein expression levels inversely correlate with metastatic potential of several cancers, which allegedly is inconsistent with the potential role of SEQ ID NO:2 in cancer.

A specification is presumed to be enabling and the U.S. Patent and Trademark Office (PTO) has the burden of establishing a *prima facie* case of lack of enablement. *See, In re Angstadt,* 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); *In re Marzocchi,* 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). To make a *prima facie* case of lack of enablement, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to

enable one of ordinary skill in the art to make and use the claimed invention. *In re Angstadt,* 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The mere fact that some experimentation is necessary does not negate enablement as long as undue experimentation is not required. *See* M.P.E.P. § 608.01(p).

The burden is on the PTO to establish that experimentation would be undue, *Angstadt,* 190 U.S.P.Q. at 219, taking into consideration the eight factors that are to be considered in determining whether a disclosure requires undue experimentation. *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Applicants submit that the amount of experimentation which may be required to practice the present invention does not rise to the level of being undue experimentation, as defined by the Court in *Wands.*

Like the production of monoclonal antibodies, the identification or production of DNA encoding a TSPAN-7 polypeptide having biological activity may require some experimentation, but if viewed in the light of *Wands*, this experimentation is not undue. Furthermore, the present applicants provide extensive guidance to allow one of ordinary skill in the art to obtain DNA that is within the scope of the claims. A biological activity of relevance here is the ability to specifically bond to antibodies that recognize at least one extracellular domain of TSPAN-7, SEQ ID NO:13 and 14. (Specification at page 7, lines 10-26.)

An analysis of the eight *Wands* factors in reference to the present invention leads to the conclusion that, viewed from the perspective of one of skill in the art, undue experimentation would not be not required to practice the claimed invention.

1. *Quantity of experimentation necessary.* One of ordinary skill in the art can construct a hybridization probe based on the disclosed polynucleotide, SEQ ID NO:2, and use the probe to locate and obtain hybridizing DNA. The polypeptide encoded by the hybridizing DNA would be tested for TSPAN-7 activity as claimed, and homology with the polynucleotide of SEQ ID NO:1 would be evaluated based on the claim language. If the results of these tests were positive, the polynucleotide sequence would fall within the scope of the claims. Such tests would not constitute "undue" experimentation within the scope of *Wands*. To determine if a polynucleotide falls within the scope of the claims, the only experimentation required is the performance of routine transfecting and assay procedures. These procedures are routine and would not have to be done repeatedly before a clear result was obtained. Because the inventors and the art provide means for the objective measurement of a polynucleotide falling

within the claim scope, this factor is met, for example, by the ability of the polynucleotide to encode a protein capable of binding to an antibody that specifically recognizes TSPAN-7 of SEQ ID NO:2. This is described in the specification at page 7, lines 10-25, and page 45, line 1 to page 50, line 17.

The *Wands* court found that practitioners in the art are prepared to screen hybridomas to find one that made the desired antibody. (8 USPQ2d at 1406.) The court further stated that an "experiment" was not simply the screening of a simple hybridoma, but instead was the entire attempt to make a monoclonal antibody against a particular antigen. This process included immunizing animals, fusing lymphocytes from the immunized animals to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas. (8 USPQ2d at 1406.)

Performing such laboratory tests is not by its nature undue experimentation. A single experiment or, more appropriately, a procedure in the present art could include obtaining or constructing a polynucleotide, expressing the polypeptide, and determining if the polypeptide binds to an antibody specific for TSPAN-7.

2. *Amount of direction or guidance provided.* The specification provides clear directions for performing the experimentation, and cites to published scientific articles for details not mentioned in the specification. Similarly, the *Wands* court found that the starting material was available to the public (as is the material used in the present application) and the patent at issue in *Wands* provided a detailed description of the methods, which included use of a commercially available kit. (8 USPQ2d at 1404, 1405.) The inventors have provided a protein that can be used to generate antibodies, which will recognize other polypeptides that fall within the scope of the claims (page 45, line 1 to page 47, line 27).

3. *Presence of absence of working examples.* The application provides the amino acid sequence and polynucleotide sequence of the claimed TSPAN-7 protein. Methods of making antibodies to proteins are provided. The inventors also designed and performed experiments to determine how cells would react to inhibition of TSPAN-7. SW620 cells were chosen because these cells can be transfected with antisense oligonucleotides, allowing the investigator to detect changes in gene expression resulting from disruption of TSPAN-7 expression. Antisense oligonucleotides capable of specifically binding to TSPAN-7 reduced TSPAN-7 messenger RNA (mRNA) and also reduced SW620 cell proliferation. These results

showed that (a) it is possible to connect an inhibition of TSPAN-7 with processes associated with TSPAN-7 activity, and (b) it is possible to *selectively* inhibit TSPAN-7 mRNA levels and protein levels. This selective inhibition is achieved using antisense oligonucleotides that specifically recognize and hybridize with TSPAN-7 sequences of the invention.

These experiments also show that it is routinely possible to detect the effect of TSPAN-7 inhibition. This can be accomplished by transfecting SW620 cells with an antisense oligonucleotide, lysing the cells after a period of incubation, and analyzing TSPAN-7 protein content using antibodies, and activity of a reporter gene, specifically a LEF1 reporter. These experiments provide an objective way of measuring TSPAN-7 content.

4. *Nature of the invention.* The invention relates to human polynucleotides. Methods of synthesizing, isolating, mutating, manipulating, transfecting, and expressing polynucleotide are the basis for the biotechnology industry, as well as the production of specific antibodies. The nature of the invention is such that it is well-known to those of ordinary skill in the art. The court in *Wands* stated that the nature of monoclonal antibody technology is that it involves screening, including screening of negative samples (in that case, hybridomas). The number of potentially negative samples was not viewed as a determining factor in reaching a finding of undue experimentation (8 USPQ2d at 1406-1407). The inventors have, for the first time, identified and cloned a human polynucleotide encoding TSPAN-7. TSPAN-7 is a member of the NET superfamily of proteins, and is believed to play a role in cell signaling processes. (Specification at page 6, lines 16-20.) Thus, it is an important protein from the perspective of its role in normal cell function. In addition, because NET protein expression is altered in cancer, and TSPAN-7 expression is elevated in prostate cancer cells, TSPAN-7 also implicated in cancer.

5. *The state of the prior art.* The prior art provides the methods and materials needed to apply the methods of factor (4) above to this group of polynucleotide, specifically TSPAN-7 polynucleotides. The *Wands* court found that "all the methods needed to practice the invention were well-known." (8 USPQ2d at 1406.) Similarly, the procedures for transfecting cells, expressing protein, and detecting antibody binding are routine and well known.

6. *The relative skill of those in the art.* Those of skill in this art are highly skilled and competent at designing and performing, or directing the performance of, the

procedures of factors (4) and (5) above. The *Wands* court found that the level of skill in the monoclonal antibody art was high at the time the application was filed, but, importantly, the court found that development of skill in performing specific experiments relevant to the art did not preclude enablement. Specifically, the court stated that initial failures occurred as the inventors learned to fuse cells, and "[o]nce they became skilled in the art, they invariably obtained numerous hybridomas . . ." that met the claim limitations. (8 USPQ2d at 1406.) By analogy, it would not defeat enablement for one of skill in the art of DNA transfection and expression to learn and become proficient in techniques for practicing the present invention.

7. *The predictability or unpredictability of the art.* One of skill, being acquainted with the methods described in the application, would predict that when a "test" polynucleotide is expressed as a protein, the ability of the protein to either bind or not bind to an antibody specific for TSPAN-7 will be capable of objective assessment. The person of skill, testing other polynucleotides as claimed, would predict that the outcome would reflect the ability of the test polynucleotide to encode a protein having structural similarity to TSPAN-7, and that this would be the only variable affecting the results. Those skilled in the art are also acquainted with the use of controls to account for variations in experimental conditions that can affect the results.

In *Wands*, the Court noted that the cell fusion technique was well known to those of ordinary skill in the art, and that there was no indication that the fusion step should be more difficult or unreliable for the antigen in question (HBsAg) than for other antigens. Finally, expressing a polypeptide and measuring antibody binding is known, and the Examiner has provided no evidence that the testing would be "more difficult or unreliable" (8 USPQ2d at 1406) than for such testing with other members of the NET protein family, or other cell membrane proteins generally.

8. *The breadth of the claims.* Using materials and methods routinely available at the time of filing, one of skill can routinely identify or construct any nucleic acid molecule meeting the limitations of the claims, and test it for activity as described for the previous factors.

In view of the foregoing remarks, applicants submit that the Examiner has not met his burden of making a *prima facie* showing that undue experimentation is required in order to

practice the invention as claimed. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 23, 25-35, 37 and 38 are rejected under 35 U.S.C. § 102(a) as being anticipated by Ruben *et al.*, WO 99/58660. The Examiner asserted that the polynucleotide of Ruben encodes a protein that is 99.63% identical with SEQ ID NO:2, with a conservative mismatch at amino acid residue 27. Applicants provide herewith an alignment of Ruben's SEQ ID NO:20 with SEQ ID NO:2, as Exhibit 1. Wherein the identity is shown to be 88%, taking into account portions of the Ruben sequence not present in TSPAN-7. Reconsideration and withdrawal of the rejection are respectfully requested.

All the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
Christoph Reinhard et al.
Davis Wright Tremaine LLP

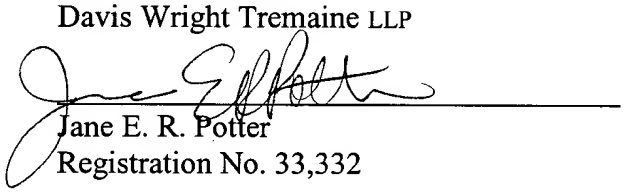

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EXHIBIT 1

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Score =  489 bits (1259), Expect = e-136
Identities = 239/270 (88%), Positives = 240/270 (88%), Gaps = 1/270 (0%)
 Frame = +1
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Sbjct: 178 MHYYRYSNAKVSCWYKYLLFSYNIIFXLAGVVFLGVGLWAWSEKGVLSDLTKVTRMHGID 357
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Gapped
Lambda     K      H
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Number of extensions: 4935
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Number of sequences better than 10.0: 2
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Number of HSP's gapped (non-prelim): 1
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X2: 129 (49.7 bits)
X3: 129 (49.7 bits)
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S1: 40 (21.7 bits)
S2: 80 (35.4 bits)
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